REMARKS

In view of the above amendments and the following remarks, the Examiner is respectfully requested to withdraw the rejections, and allow claims 59, 60, 62, 63, 72-74, 77-85, the currently pending claims. Claims 1-58, 61, 64-71, and 75-76 are canceled. Claims 59, 62, 63, 72-73 and 77-79 are amended. Claims 80-85 are added. No new matter is added. Applicants respectfully request reconsideration of the rejections.

Claim 59 is objected to as being drawn to a non-elected species. Applicants respectfully submit that the claim is properly maintained. In the Restriction Requirement, the cell-specific TRE were stated to be a species election. Applicants elected the species, prostate specific TRE. The generic claims are therefore held in abeyance until such time as a species claim is deemed allowable, at which time the generic claim will be considered. Withdrawal of the objection is requested.

Claims 59, 60, 62, 63, 72-75 and 76-79 have been rejected under 35 U.S.C. 112, second paragraph. The Office Action states that the omitted element is: "what is the target of the adenovirus vector and how is the adenovirus vector suppressing tumor growth in an individual if the claim does not define where it is administered. The claim does not complete the preamble, which encompasses a method for suppressing tumor growth in an individual."

The claims have been amended in accordance with the Examiner's suggestions to insert the phrase "to a mammal". The target of the adenovirus is the tumor cells, which has been clarified in the claims. The virus is administered to a mammal, but the specific site of administration is not essential to the invention, because the adenovirus does not replicate in non-targeted cells. For example, administration can be intravenous, as previously discussed. In view of the above amendments and remarks, withdrawal of the rejection is requested.

Applicants note that independent Claim 77 is free of art rejections. Currently pending claims 72-74 and 78-80 have been amended to depend from Claim 77, and therefore are also free of the art. Further, Claim 59 (and therefore its dependent claim 60) has been rewritten to recite "a synergistic combination" of adenovirus and chemotherapeutic compound, and therefore is a generic equivalent of Claim 77. In view of the amendments, withdrawal of the rejections is requested.

Claims 62, 63 and newly added claims 81-85 stand rejected under the cited combination of prior art, as obvious in view of as unpatentable in view of Henderson *et al.*, U.S. 5,871,726; taken with Gurnani *et al.*, or further in view of Duque *et al.* Applicants respectfully submit that the present claims are not taught or suggested by the cited combination of references.

Henderson *et al.* teaches a cell-specific, replication competent adenovirus, but does not teach the benefits of a combination immunotherapy. One of skill in the art could not predict the effects of combining a chemotherapeutic agent with such an adenovirus, because the killing effect of the drug could have reduced the ability of the virus to lyse cells, rather than providing for a combined benefit. In the absence of Applicants teachings, it could not have been predicted that a beneficial result would have been obtained.

Gurnani *et al.* teach the use of replication deficient adenovirus as a means of gene therapy. The adenovirus does not replicate and cause cytolysis of the host cell; it is merely a means of delivering the gene of interest – a p53 tumor suppressor gene under the control of a cytomegalovirus promoter.

Gurnani *et al.* describe the results of animal model studies using: (1) an ovarian cancer model where a "3 drug" combination of Ad-p53 + cisplatin and paclitaxel reported as efficacious; (2) a prostate cancer model where a "2 drug" combination was reported as efficacious (Ad-p53 + cisplatin); (3) a mammary tumor model where a "2 drug" combination was reported as efficacious (Ad-p53 + cisplatin); and (4) a head/neck cancer model where a "2 drug" combination was reported as efficacious (Ad-p53 + 5-FU).

The present claims are directed to combinations of a replication deficient adenovirus and an antineoplastic agent selected from the group consisting of paclitaxel, docetaxel, doxorubicin and etoposide) + adenovirus for treatment of prostate cancer (cl 77); liver cancer (AFP-TRE; cl 59) and bladder cancer (UPII; cl 59), none of which are suggested by Gurnani *et al.* The present claims do not encompass cisplatin or 5-FU, the basis for the positive results provided in Gurnani *et al.*

Further, one cannot extrapolate from the replication deficient adenovirus of Gurnani *et al.*, to the replication competent adenovirus of Henderson. The adenovirus vector taught by Gurnani does not utilize the host cell to replicate virus. As discussed above, it was uncertain that, in the presence of a lethal chemotherapeutic drug, the adenovirus would be able to replicate and provide for a beneficial combination.

The underlying mechanisms of action are completely different between the methods taught by Gurnani and the presently claimed invention. One of skill in the art would not be able to predict the effect of a replication competent cytolytic adenovirus, based on extrapolation from the prior art adenoviral vector, which is not replication competent, not cell-specific and not cytolytic. The

effectiveness of the presently claimed combination could not have been predicted by the results of the data obtained with an unrelated adenoviral entity.

The citation of Duque *et al.* is provided for teaching the deletion of the 19 Kd region in the adenovirus E1B gene. Applicants respectfully submit that Duque *et al.* does not remedy the deficiencies of the primary references. One of skill in the art would not have been able to predict that the adenovirus as set forth in the present claims would effectively replicate and cause cytolysis of tumor cells when the tumor cells are also exposed to anti-neoplastic drugs, because the adenovirus activity relies on selective replication in the targeted host cells. The deletion of the 19 kDA region does not alter the requirement of a host cell for adenovirus replication. Duque *et al.* fails to make up for the deficiency in the primary references and does not teach or suggest that a combination therapy as set forth in the claims would be effective, or could have a synergistic effect.

CONCLUSION

Applicants submit that all of the claims are now in condition for allowance, which action is requested. If the Examiner finds that a Telephone Conference would expedite the prosecution of this application, she is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any other fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815, order number CELL-017.

Respectfully submitted,

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